

Appln. No. 09/763,293
Amd. dated April 14, 2004
Reply to Office Action of October 14, 2003

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-3 (Cancelled)

4 (Currently amended). A synthetic anti-inflammatory peptide of IL-2 or an anti-inflammatory derivative thereof, which inhibits in vitro: (i) adhesion of activated T cells to fibronectin, laminin and/or collagen-type IV; (ii) chemotactic migration of T cells through fibronectin; and/or (iii) spontaneous or TNF- α -induced secretion of IL-8 or IL-1 β , from intestinal epithelial cells according to claim 3, selected from the group consisting of:

(i) peptides **pep1**, **pep2**, and **pep3** of the sequences:

(**pep1**) Ile-Val-Leu

(**pep2**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1)

(**pep3**) Arg-Met-Leu-Thr (SEQ ID NO:2)

(ii) peptides obtained from **pep2** by deletion of one or more amino acid residues;

(iii) peptides obtained by addition to peptides (i) or (ii) of one or more natural or non-natural amino acid residues to the N-terminus and/or C-terminus;

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(iv) peptides obtained by replacement of one amino acid residue of peptides (i) to (iii) by another natural amino acid residue or by a non-natural amino acid residue;

(v) peptides of (i) to (iii) which are all-L, all-D or a combination of D- and L- amino acid residues.

(vi) chemical derivatives of the peptides (i) to (v), wherein the chemical derivatives are derivatives in which additional chemical moieties not normally part of the peptides are present;

(vii) cyclic derivatives of peptides (i) to (vi);

(viii) dual peptides consisting of two of the same or different peptides (i) to (vii), wherein the peptides are covalently linked to one another directly or through a spacer; and

(ix) multimers ~~comprising~~ consisting of a ~~number~~ plurality of the same or different peptides (i) to (viii).

5(Currently amended). The synthetic peptide Ile-Val-Leu (pep1) and derivatives thereof according to claim 4, obtained by:

(a) elongation by up to 3-4 further amino acid residues at the N- and/or C-terminal, ~~preferably according to the natural sequence of IL-2;~~

(b) substitution of the Ile residue by a natural or non-natural amino acid hydrophilic polar neutral or negatively charged, or hydrophobic non-polar neutral amino acid residue, ~~preferably selected from Glu, Asp, Asn, Gln, Ala, Val;~~

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(c) substitution of the Val residue by a hydrophobic, non-charged natural or non-natural amino acid residue, ~~preferably selected from Ala, Ile, Leu, Met, Nle, Phe;~~

(d) substitution of the Leu residue by a hydrophobic, non-charged natural or non-natural amino acid residue, ~~preferably selected from Ala, Ile, Met, Nle, Phe, Val;~~

(e) amidation of the C-terminal Leu residue,

(f) cyclization of **pep1** or of any peptide of (a) to (e); and

or

(g) any combination of (a) to (f).

6(Currently amended). A synthetic peptide according to claim 5, selected from the group consisting of:

(**pep1**) Ile-Val-Leu

(**pep4**) Asn-Ile-Asn-Val-Ile-Val-Leu (SEQ ID NO:3),

(**pep5**) Ile-Val-Leu-Glu-Leu-Lys-Gly (SEQ ID NO:4),

(**pep6**) Asn-Val-Ile-Val-Leu (SEQ ID NO:5)

(**pep7**) Ala-Val-Leu

(**pep8**) Ile-Ala-Leu

(**pep9**) Ile-Val-Ala

(**pep10**) Glu-Val-Leu

(**pep11**, linear) and (**pep12**, cyclic) Cys-Ile-Val-Leu-Ala-Cys (SEQ ID NO:6) and,

(**pep13**, linear) and (**pep14**, cyclic) Cys-Ile-Val-Leu-Ala-Ala-Cys (SEQ ID NO:7).

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7 (Currently amended). The synthetic peptide Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1) (**pep2**), and derivatives thereof according to claim 4, obtained by:

(a) elongation at the C- and/or N-terminal ends by up to 4 further amino acid residues total, ~~preferably according to the natural sequence of IL-2;~~

(b) substitution of the Glu residue by a natural or non-natural charged or polar charged amino acid residue, ~~preferably selected from Lys, Arg, Asp, Gln, Asn;~~

(c) substitution of the Phe residue by a natural or non-natural hydrophobic aliphatic or aromatic amino acid residue, ~~preferably selected from Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, Nle;~~

(d) substitution of the Leu residue by a natural or non-natural hydrophobic aliphatic or aromatic amino acid residue, ~~preferably selected from Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, Nle;~~

(e) substitution of the ~~important~~ Asn residue by a hydrophilic, non-charged, aliphatic natural or non-natural amino acid residue ~~such as Gln;~~

(f) substitution of the Arg residue by a positively charged, natural or non-natural amino acid residue, ~~preferably selected from Lys, Orn, homoArg;~~

(g) substitution of the Trp residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue, ~~;~~

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~~preferably selected from Tyr, Ile, Leu, Nle, Tie, Phe, 4-phenyl Phe,
4-methyl Phe;~~

(h) substitution of the Ile residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue,
~~preferably selected from Tyr, Phe, Leu, Nle, Tie;~~

(i) substitution of the Thr residue by an aliphatic hydrophobic amino acid residue ~~such as Ala, Ile, Leu,~~ or a hydroxy- or thio-containing amino acid residue ~~preferably selected from Cys, Ser;~~

(j) truncation by up to 4 amino acid residues from either the C or N terminal;

(k) amidation of the C-terminal Thr;

(l) cyclization of **pep2** or of any peptide of (a) to (k);

and or

(m) any combination of (a) to (l).

8(Currently Amended). A peptide according to claim 7, selected from the group consisting of:

(**pep2**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1)

(**pep15**) Ile-Val-Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:8)

(**pep16**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Phe-Cys (SEQ ID NO:9)

(**pep17**) Ala-Thr-Ile-Val-Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:10)

(**pep18**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Phe-Cys-Gln-Ser (SEQ ID NO:11)

(**pep19**) Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:12)

(**pep20**) Arg-Trp-Ile-Thr (SEQ ID NO:13)

(**pep21**) Glu-Phe-Leu-Asn (SEQ ID NO:14)

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(**pep22**) Ala-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:15)
(**pep23**) Lys-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:16)
(**pep24**) Glu-Ala-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:17)
(**pep25**) Glu-Val-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:18)
(**pep26**) Glu-Phe-Ala-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:19)
(**pep27**) Glu-Phe-Leu-Ala-Arg-Trp-Ile-Thr (SEQ ID NO:20)
(**pep28**) Glu-Phe-Leu-Asn-Ala-Trp-Ile-Thr (SEQ ID NO:21)
(**pep29**) Glu-Phe-Leu-Asn-Glu-Trp-Ile-Thr (SEQ ID NO:22)
(**pep30**) Glu-Phe-Leu-Asn-Arg-Ala-Ile-Thr (SEQ ID NO:23)
(**pep31**) Glu-Phe-Leu-Asn-Arg-Trp-Ala-Thr (SEQ ID NO:24)
(**pep32**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Ala (SEQ ID NO:25)
(**pep33**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-NH₂ (SEQ ID NO:26) and,
(**pep34**, linear) and (**pep35**, cyclic) Cys-Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Ala-Cys (SEQ ID NO:27).

9(Currently amended). The synthetic peptide Arg-Met-Leu-Thr (SEQ ID NO:2) (**pep3**), and derivatives thereof according to claim 4, obtained by:

(a) elongation by up to 4 further amino acid residues at the C and/or N terminal end, ~~preferably according to the natural sequence of IL-2;~~

(b) substitution of the Arg residue by a natural or non-natural positively charged amino acid residue, ~~preferably selected from Lys, Orn, homoArg, diaminobutyric acid;~~

(c) substitution of the Met residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue,—
~~preferably selected from Phe, Tyr, Ile, Leu, Nle, Tie;~~

(d) substitution of the Leu residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue,—
~~preferably selected from Phe, Tyr, Nle, Tie;~~

(e) substitution of the Thr residue by an aliphatic hydrophobic amino acid residue ~~such as Ala, Ile, Leu,~~ or a hydroxy- or thio-containing amino acid residue ~~such as Ser, Cys;~~

(f) amidation of the C-terminal Thr residue;

(g) cyclization of **pep3** or of any peptide of (a) to (f); and

or

(h) any combination of (a) to (g).

10(Currently amended). A peptide according to claim 9,
selected from the group consisting of:

- (**pep3**) Arg-Met-Leu-Thr (SEQ ID NO:2)
- (**pep36**) Ala-Met-Leu-Thr (SEQ ID NO:28)
- (**pep37**) Arg-Ala-Leu-Thr (SEQ ID NO:29)
- (**pep38**) Arg-Met-Ala-Thr (SEQ ID NO:30)
- (**pep39**) Arg-Met-Leu-Ala (SEQ ID NO:31)
- (**pep40**) Lys-Met-Leu-Thr (SEQ ID NO:32)
- (**pep41**) Arg-Val-Leu-Thr (SEQ ID NO:33)
- (**pep42**) Arg-Met-Leu-Thr-NH₂ (SEQ ID NO:34)
- (**pep43**) Pro-Lys-Leu-Thr-Arg-Met-Leu-Thr (SEQ ID NO:35)

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(**pep44**) Arg-Met-Leu-Thr-Phe-Lys-Phe-Tyr (SEQ ID NO:36) and,
(**pep45**, linear) and (**pep46**, cyclic) Cys-Arg-Met-Leu-Thr-Ala-Cys
(SEQ ID NO:37).

Claims 11-13 (Cancelled).

14(Currently amended). A pharmaceutical composition comprising at least one synthetic peptide or peptide derivative according to claim [[3]] 4, and a pharmaceutically acceptable carrier.

Claims 15-17 (Cancelled)

18(Currently amended). A method for the treatment and/or alleviation of acute and chronic inflammatory disorders comprising administering to a subject in need thereof an effective amount of an anti-inflammatory synthetic peptide according to claim [[3]] 4.

19(Previously presented). The synthetic peptide of claim 4, which is **pep2** (SEQ ID NO:1).

20(Previously presented). A pharmaceutical composition comprising the synthetic peptide of claim 19 and a pharmaceutically acceptable carrier.

21(Presently presented). A method for the treatment and/or alleviation of acute and chronic inflammatory disorders comprising administering to a subject in need thereof an effective amount of an anti-inflammatory synthetic peptide according to claim 19.

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Claims 22-24 (Cancelled).

25(New). The synthetic peptide and derivatives thereof according to claim 7, wherein:

said elongation is according to the natural sequence of IL-2;

said substitution of the Glu residue is selected from the group consisting of Lys, Arg, Asp, Gln, and Asn;

said substitution of the Phe residue is selected from the group consisting of Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, and Nle;

said substitution of the Leu residue is selected from the group consisting of Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, and Nle;

said substitution of the Asn residue is Gln;

said substitution of the Arg residue is selected from the group consisting of Lys, Orn, and homoArg;

said substitution of the Trp residue is selected from the group consisting of Tyr, Ile, Leu, Nle, Tic, Phe, 4-phenyl-Phe, and 4-methyl-Phe;

said substitution of the Ile residue is selected from the group consisting of Tyr, Phe, Leu, Nle, and Tic; and

said substitution of the Thr residue is selected from the group consisting of Ala, Ile, Leu, Cys, and Ser.

26(New). The synthetic peptide and derivatives thereof according to claim 5, wherein:

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said elongation is according to the natural sequence of IL-2;

said substitution of the Ile residue is selected from the group consisting of Glu, Asp, Asn, Gln, Ala, and Val;

said substitution of the Val residue is selected from the group consisting of Ala, Ile, Leu, Met, Nle, and Phe; and

said substitution of the Leu residue is selected from the group consisting of Ala, Ile, Met, Nle, Phe, and Val.

27(New). The synthetic peptide and derivatives thereof according to claim 9, wherein:

said elongation is according to the natural sequence of IL-2;

said substitution of the Arg residue is selected from the group consisting of Lys, Orn, homoArg, and diaminobutyric acid;

said substitution of the Met residue is selected from the group consisting of Phe, Tyr, Ile, Leu, Nle, and Tic;

said substitution of the Leu residue is selected from the group consisting of Phe, Tyr, Nle, and Tic; and

said substitution of the Thr residue is selected from the group consisting of Ala, Ile, Leu, Ser, and Cys.